Remarks

Applicants herewith submit substitute sheets of Drawings in compliance with 37 C.F.R. 1.121(d). Applicants note that identical drawings were already submitted on April 28, 2006 in connection with the Preliminary Amendment filed on the same date. Accordingly, as already indicated in the correspondence submitted on April 28, 2006, no new matter has been introduced in the substitute sheets for the drawings and their entry is respectfully requested.

Applicants have amended claims to expedite prosecution of preferred embodiments. Specifically, Applicants have amended claim 1 to explicitly state that the method is directed to human transplant recipients and donors, and that the VEGF is a human secreted VEGF. Support for the amendments can be found, for example in paragraphs [0014], [0060], and [0062]. Claim 1 has been further amended to indicate that the administration is parenteral. Support for this amendment can be found, for example, in paragraph [0066]. Claims 2, 6, 15, 30, 37 and 38 have been amended to comply with the amendments to claim 1. Applicants have amended claims 17 and 32 to correct an inadvertent typographical error in the term "Bevacizumab." Applicants have further amended claim 17 to include antibody IMC-1C11. Support for this amendment can be found, for example, in paragraph [0014]. Applicants have also added new claims 39 and 40. Support for claim 39 can be found, for example, in paragraph [0038]. Support for claim 40 can be found, for example, in paragraphs [0014] and [0075].

Accordingly, Applicants believe that no new matter has been introduced by the amendments or the new claims and their entry is respectfully requested.

The Examiner objected to claims 17 and 32 because of an inadvertent spelling error in the term "Bevacizumab." Applicants respectfully submit that the amendments to claims 17 and 32 have obviated this objection.

The Examiner rejected claims 1-7, 9, 11, 13, 15, 30, 31, 34, 37, 38 as allegedly not complying with 35 U.S.C. §112, first paragraph, written description requirement. Specifically, the Examiner alleged that "the claims encompass use of a VEGF antagonist or an antibody against VEGF as an antagonist or the generic antagonists of claim 34." The Examiner acknowledged that "murine and human VEGF of specific amino acid sequences were known in

the art." The Examiner also alleged that the claimed VEGF antagonists "encompass a vast collection of unknown agents wherein the identity of said molecules is unpredictable."

Applicants respectfully submit that the rejection should be withdrawn for the following reasons.

Applicants have amended the claims to encompass only antagonists to the known human secreted VEGF variants. As the Examiner acknowledged, the human VEGF sequences were well known to a skilled artisan at the time the application was filed. In view of the knowledge of this family of proteins, a skilled artisan, using routine techniques can easily screen for agents that inhibit these human secreted VEGF molecules. Furthermore, the method of the **invention is not directed to these agents**, but to the use of these agents in a method of preventing rejection, specifically, by **administering these agents to a donor** of the transplanted organ. The Examiner cites *Regents of the University of California v. Eli Lilly & Co.* , 119 F.3d. 1559 (Fed. Cir. 1997) wherein the court stated that when one claims a specific nucleic acid, the sequence of it must be disclosed. However, Applicants respectfully submit that the *Regents of the University of California v. Eli Lilly & Co.* dealt with **claiming an unknown compound**. Thus, in *Regents of the University of California v. Eli Lilly & Co.*, the compound was unknown. That is not what is claimed here. What Applicant claims is the use of compounds that inhibit a known protein, i.e. human secreted VEGF inhibitors, in a method for inhibiting organ transplant rejection. Thus, Applicants respectfully submit that *Regents of the University of California v. Eli Lilly & Co.* is not pertinent. The Federal Circuit has specifically dealt with the difference between claiming a class of unknown compounds and claiming a method of using compounds in Capon v. Eshhar , 418 F.3d 1349 (Fed. Cir. 2005). It is that latter situation the present claims are dealing with.

Applicants also respectfully submit that as stated by the Court in *KSR v. Teleflex Inc*, 127 S. Ct. 1727 (2007)), a person of ordinary skill in the art is also a person of ordinary creativity, not an automaton. Thus, a skilled artisan knowing the human secreted VEGF proteins is perfectly capable of screening additional compounds be they small molecules, siRNAs, antibodies or the like, that inhibit VEGF using routine methods, and then apply them according to the teachings of the present method, where such an inhibition is shown to inhibit organ rejection.

Accordingly, Applicants respectfully submit that claims 1-7, 9, 11, 13, 15, 30, 31, 34, 37, 38 now fully comply with 35 U.S.C. §112, first paragraph, written description requirement, and

thus the rejection should be withdrawn. Certainly the rejection should not apply to claims 15-17, 30-3235-36 and 40.

The Examiner rejected claims 1-4, 6, 7, 9, 11, 34, 36 and 38 under 35 U.S.C. §102(b) as allegedly anticipated by Armstrong et al. (U.S. Patent No. 5,547,959)("Armstrong").

Applicants respectfully disagree and submit that the rejection should be withdrawn for the following reasons.

Armstrong does not teach *in vivo* treatment of an organ donor **prior to donation** of the organ. Armstrong specifically teaches that one treats the **donor organ *ex vivo*** both when the organ, in their case blood, is derived from the subject himself and when the organ is derived from a different donor animal.

The present claims require parenteral administration of the human sectered VEGF antagonist. Accordingly, Applicants respectfully submit that Amstrong does not disclose all the elements of the claimed invention and thus the rejection under 35 U.S.C. §102(b) is improper and should be withdrawn.

The Examiner rejected claims 1-7, 9, 11, 15, 30, 31, 34, 36-38 under 35 U.S.C. §103(a) as allegedly obvious over Armstong in view of Feldmann et al. (WO 98/51344)("Feldmann").

Applicants respectfully disagree and submit that the rejection should be withdrawn for the following reasons.

As discussed above, Armstrong does not teach one essential element of the claims, namely, that the administration is performed parenterally to the donor. Feldman does not overcome this deficiency. Feldman describes administering the agent to the recipient individual, not the donor. Accordingly, the combination of the references fails to teach all the elements of the claims.

Therefore, the rejection of claims 1-7, 9, 11, 15, 30, 31, 34, 36-38 under 35 U.S.C. §103(a) over Armstong in view of Feldmann should be withdrawn.

The Examiner rejected claims 1-7, 9, 11, 15, 30, 31, 34, 36-38 under 35 U.S.C. §103(a) as allegedly obvious over Armstong in view of Feldmann and further in view of Cutler et al. (U.S. 2003/0185831)("Cutler").

Applicants respectfully disagree and submit that the rejection be withdrawn for the following reasons.

As already discussed above, the combination of Armstrong with Feldmann does not teach all the elements of the claims, namely, that it is the donor who receives the agent parenterally prior to the organ harvest or organ donation. Cutler does not overcome this deficiency. Cutler only describes using Bevazymab in the treatment of the organ recipient, not the donor.

Accordingly, Applicants respectfully submit that the rejection of claims 1-7, 9, 11, 15, 30, 31, 34, 36-38 under 35 U.S.C. §103(a) over Armstong in view of Feldmann and further in view of Cutler should be withdrawn.

The Examiner also rejected claim 35 under 35 U.S.C. §103(a) as allegedly obvious over Armstong in view of Feldmann and further in view of Wood et al. (U.S. 2006/0270665)("Wood").

Also Wood does not describe the missing element from the combination of Armstrong and Feldmann, namely, that it is the donor who receives the agent parenterally prior to the organ harvest or organ donation. Wood only describes treatment of kidney allograft recipient with PTK787.

Accordingly, Applicants respectfully submit that the rejection of claim 35 under 35 U.S.C. §103(a) over Armstong in view of Feldmann and further in view of Wood should be withdrawn.

The Examiner further rejected claim 13 under 35 U.S.C. §103(a) as allegedly obvious over Armstong in view of Feldmann and further in view of Neville et al. (US 2005/0142117)("Neville").

Also Neville fails to describe the missing element from the combination of Armstrong and Feldmann, namely, that it is the donor who receives the agent parenterally prior to the organ harvest or organ donation. Neville only describes use of mycophenolate mofetil as an immunosuppressive agent.

Accordingly, Applicants respectfully submit that the rejection of claim 13 under 35 U.S.C. §103(a) over Armstong in view of Feldmann and further in view of Neville should be withdrawn.

Accordingly, there is nothing in the combination of any of the references that would teach or suggest or let a skilled artisan to expect success in a method for inhibiting transplant rejection by parenterally administering to an organ donor a human secreted VEGF antagonist.

In view of the foregoing, Applicants respectfully submit that all claims are in condition for allowance. Early and favorable action is requested.

In the event that any additional fees are required, the Commissioner is hereby is authorized to charge our deposit account No. 50-0850. Any overpayments should also be deposited to said account.

Date: January 26, 2009

Respectfully submitted,

/Leena H. Karttunen/

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